# Cancer and sepsis: future challenges for long-term outcome

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**Purpose of review**
The purpose of this review is to investigate the long-term outcomes of cancer patients who experience sepsis or septic shock.

**Recent findings**
Sepsis is a frequent cause of ICU admission in cancer patients, accounting for approximately 15% of such cases. Short-term mortality rates among these patients vary widely across studies, but they are consistently found to be slightly higher than those of noncancer patients. However, there is a lack of evidence regarding the long-term outcomes of cancer patients who have experienced sepsis or septic shock. The few available studies have reported relatively high mortality rates, reaching around 80% in a few cohort studies. Although several observational studies have noted a decrease in 1-year mortality rates over time, observational data also suggest that sepsis may increase the risk of cancer in the long run.

**Summary**
As cancer is becoming a chronic disease, there is an urgent need for studies on the quality of life of cancer patients who have experienced sepsis. The relationship between sepsis and cancer extends beyond its impact on the progression of cancer, as sepsis might also contribute to the development of cancer.

**Keywords**
cancer, mortality, outcome, quality of life, sepsis, shock

## INTRODUCTION

Cancer has the highest impact on cause-specific disability-adjusted life years, with the risk of developing cancer from age 0 to 74 years estimated to be around 20% [1]. In 2020, cancer accounted for one in six deaths, resulting in 10 million premature deaths worldwide [2].

In patients with cancer, both the disease itself and the complications associated with its management are frequent causes of admission to the ICU. Currently, there is no debate about the need to admit cancer patients to the ICU [3]. In an international observational study involving 15 165 ICU patients, cancer was reported as a comorbidity in 16.7% of cases, with solid cancers comprising 13.5% and hematologic malignancies 2.8% of cases, making it the most common comorbidity is this large study [4]. A French observational study based on the national health insurance general scheme found that active cancer was reported in around 10% of 133 966 patients admitted to the ICU. Active cancer was associated with increased hospital mortality, with an odds ratio (OR) of 1.36 and a 95% confidence interval (CI) of 1.24–1.49. This elevated mortality persisted at 3 years (2.72; 95% CI 2.59–2.86) among ICU survivors [5]. Based on a meta-analysis of 7354 ICU patients with cancer, hospital mortality decreased from 2005 to 2015, even after adjusting for confounders (OR for hospital mortality per year: 0.96; 95% CI 0.95–0.97) [6]. Thus, cancer patients represent a significant burden in the ICU. However, although they still experience increased mortality, significant progress in the management of these patients has been observed following ICU admission.

Meanwhile, sepsis is defined as an infection associated with organ dysfunction, as indicated by an increase in the sequential organ failure assessment (SOFA) score. There is a continuum of severity from sepsis to septic shock, which is defined as sepsis requiring vasopressor support and a serum lactate

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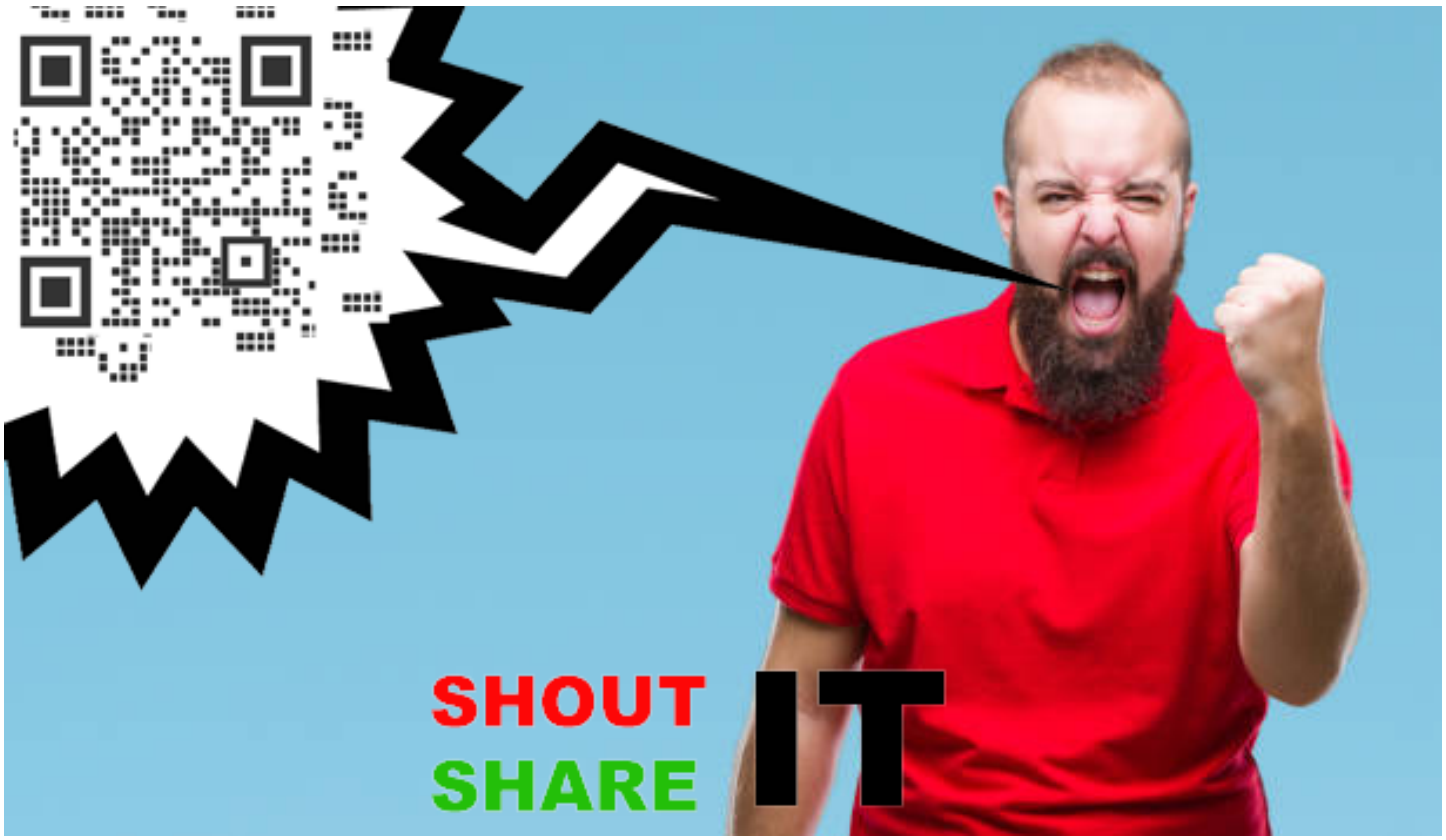
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## KEY POINTS

- Cancer and sepsis interplay in a large number of ICU patients, whose outcomes are affected both by cancer and sepsis.
- Data extracted from a large database reported encouraging results in terms of short-term mortality rates in patients with cancer and sepsis, although long-term outcomes remain poor in cancer patients who have experienced septic shock.
- Long-term outcomes of cancer patients should be investigated in future studies because cancer is becoming, due to emergent treatments, a chronic disease.
- Sepsis survivors may be more susceptible to cancer than the general population, although future studies are required to confirm this observation.

concentration above 2 mmol/l. The definitions of sepsis and septic shock are applicable to cancer patients just as they are to the general population [7]. Sepsis also imposes a significant burden in terms of global morbidity and mortality [8]. In 2017, a worldwide analysis estimated a sepsis incidence of 48.9 million cases, resulting in 11 million deaths, accounting for 19.7% of all global deaths [9]. In the general population, septic shock is associated with a hospital mortality rate of around 45% [10].

## SEPSIS AND CANCER

Immune dysfunction related to cancer and its treatments, along with neutropenia, chemotherapy, and exposure to invasive procedures, are risk factors for developing sepsis (Fig. 1). Numerous studies have highlighted a high prevalence of sepsis among cancer patients. According to a US health claims database covering the period from 2005 to 2014 and including 119 379 patients newly diagnosed with sepsis who underwent chemotherapy, 2560 (2.1%) developed sepsis, 477 (0.3%) experienced severe sepsis, and 1331 (0.1%) progressed to septic shock within 1 year [11]. A retrospective study utilizing statewide Victorian Cancer Registry data reported a sepsis incidence of 6.4% during the first year after cancer diagnosis, representing 13 316 patients, of whom 29% required ICU admission [12].

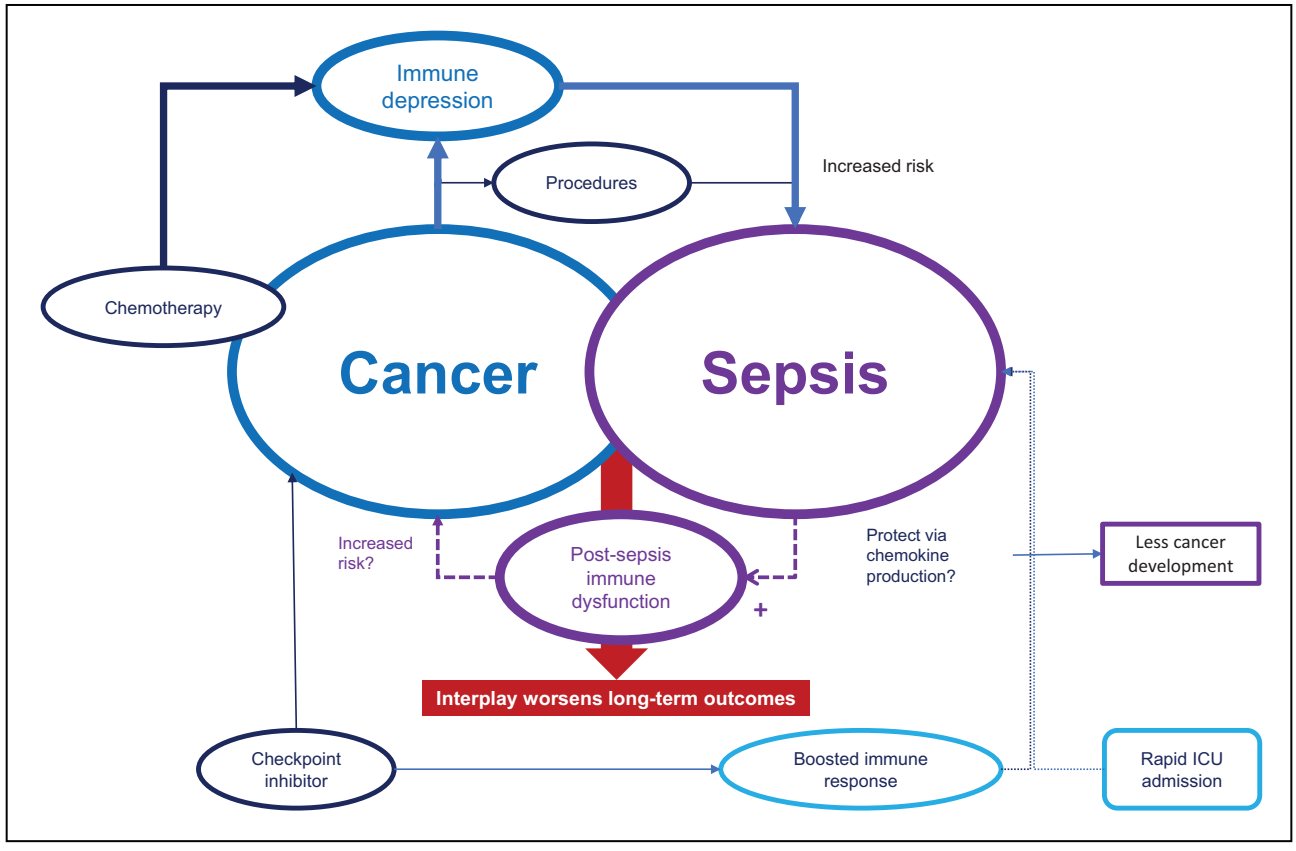


**FIGURE 1.** Interplay between cancer and sepsis. Cancer, per se and due to chemotherapy and invasive procedures, is associated with immune depression favoring the occurrence of sepsis and impairing the long-term outcomes of patients with sepsis. In contrast, sepsis may be the cause of immune dysfunction associated with the development of cancer.



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In a prospective, multicenter study assessing reasons for ICU admission in Brazil, Soares *et al.* [13] found that sepsis accounted for 15% of cancer patients, ranking as the second most common reason for ICU admission after postoperative care. This observation aligns with findings from a national cross-sectional survey conducted in 44 Chinese ICUs, which identified solid cancer and hematologic malignancies in 12.3 and 1.8% of patients with sepsis, respectively [14]. Conversely, a nationwide study in Iceland revealed that 24% of patients admitted to the ICU for sepsis had cancer, with hospital-acquired infections being more prevalent among these patients than among noncancer patients [15▪].

In summary, cancer patients comprise approximately 10% of hospitalized individuals and about one in five sepsis admissions. In the ICU, sepsis is the second leading cause of admission among these patients.

## METHODS

In the following, we will discuss the recent literature on the relationship between cancer and sepsis in terms of outcomes. Using PubMed, we selected recent articles using the following key words: 'sepsis', 'septic shock', 'cancer', 'intensive care', 'outcome', 'mortality', and 'quality of life'. We considered publications in English, recent studies (<15 years), as well as those reporting outcomes of large patient cohorts.

### Short-term mortality

Sepsis has been identified as a potential cause of death among cancer patients [16]. Numerous observational studies have examined the mortality rates of cancer patients who develop sepsis and septic shock. A recent meta-analysis, which reviewed 10 studies on cancer and sepsis, involving 6605 patients aged from 51.4 to 64.9 years, found pooled ICU, hospital, and 28–30-day mortality rates of 48% (95% CI 43–53%; $I^2 = 80.6\%$), 62% (95% CI 58–67%; $I^2 = 0\%$), and 50% (95% CI 38–62%; $I^2 = 98\%$), respectively. The authors concluded that cancer patients with sepsis have high mortality rates, but they emphasized the large variability between studies [17▪▪]. This variability could be related to differences in the sepsis definitions used across different studies, heterogeneity in critical care practices globally, and variations in healthcare system-dependent levels of care.

To mitigate this bias, we focused our research on studies utilizing large national databases. For instance, the US National Readmissions Database, covering 27 481 517 hospitalizations from 2013 to 2014, showed an in-hospital mortality rate of 27.9% among cancer patients with sepsis, compared with 19.5% in noncancer patients with sepsis, resulting in an adjusted absolute increase ranging from 2.2 to 15.2% [18]. Notably, this disparity was more pronounced in younger adults and tended to diminish with age. In another large cohort of cancer patients, the hospital mortality rates of those with sepsis, severe sepsis, and septic shock were 14.8, 30, and 46% respectively, in alignment with the short-term outcomes reported in a previous study [11].

Small cohorts of cancer patients provide valuable insights into individual trajectories. In a well documented cohort from a single center in Texas, among 271 solid cancer patients admitted to ICU for septic shock, the 28-day mortality rate was 69.4%. Factors independently associated with mortality included metastatic disease, respiratory failure, elevated lactate levels, and an Eastern Cooperative Oncology Group performance status of 3 or 4. This high mortality rate may be attributed to the stringent application of the sepsis-3 definition in this population. Correspondingly, among the 545 patients who had sepsis and required vasopressors but did not meet the sepsis-3 criteria, the 28-day mortality rate was 33.6% [19▪].

Short-term mortality in patients with septic shock is typically assessed using ICU, hospital, or 28–30-day mortality rates. Lemiale *et al.* [20] demonstrated that mechanical ventilation and vasopressor use were independent factors associated with short-term mortality, although survival improved over time. Although large-scale studies based on databases may suggest that short-term mortality rates among cancer patients with sepsis and septic shock fall within a reasonable range as compared with noncancer patients, a closer examination of available data indicates that cancer patients with septic shock still face a higher risk of short-term mortality than noncancer patients.

### Long-term mortality

The long-term outcomes of ICU patients with solid cancer or hematologic malignancies remain poorly documented. A recent Canadian prospective study followed 414 patients with hematologic malignancies. In this cohort, respiratory failure (50%) and sepsis (40%) were the most common reasons for ICU admission. At the 12-month mark, 21% of the entire cohort and 43% of patients discharged alive from the ICU survived, with rates ranging from 28% for the patients with lymphoma/multiple myeloma/other to 12% for those with allogenic hematopoietic cell transplantation. However, mortality rates improved when only ICU survivors were considered.



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Notably, in this study, sepsis was not an independent factor for 1-year mortality [21]. Key takeaways from this observational study included the following: only one in five patients survive 1 year after ICU admission in the context of hematologic malignancies; long-term outcomes differ between all patients admitted to the ICU and those surviving at the ICU discharge, requiring specific research in the latter group; and the type of cancer is the main determinant of long-term outcomes.

In a Korean registry study, the 2-year mortality rate of 5449 adult cancer patients with septic shock requiring renal replacement therapy was 85.1%. Older age, higher comorbidity Charlson index, and hematologic cancer were associated with higher 2-year mortality rate [22]. This follow-up was one of the longest in this population of cancer patients with septic shock. Camou *et al.* prospectively followed 496 patients admitted to the ICU for septic shock, including 252 with cancer (119 with hematologic malignancies and 133 solid tumors). Several findings from this study are noteworthy. First, as expected, the rate of decisions to forgo life-sustaining therapy was higher among cancer patients than noncancer patients (52 versus 39%). On day 180, the mortality rates were 44, 51, and 68% in noncancer patients, those with hematologic malignancies, and those with solid cancer, respectively. Multivariate analysis identified performance status, the Charlson Comorbidity Index, severity scores, and the decision to forgo life-sustaining therapy as independent predictors of 180-day mortality [23]. In another single-center prospective cohort comprising 132 cancer patients requiring vasopressors due to sepsis, the mortality rates at day 28 and 1 year were 60.6 and 83.3%, respectively [24]. A retrospective, single-center study involving 1408 cancer patients reported mortality rates of 74, 78.9, and 83.2% at the 3 months, 6 months, and 1 year, respectively [25]. Finally, in a cohort of 259 cancer patients requiring surgery, postoperative sepsis ($n = 77$) was identified as a risk factor for mortality during the follow-up period (34 months from ICU admission). Notably, 10 (63%) out of 16 deaths due to postoperative sepsis were related to cancer recurrences [26]. However, these single-center, retrospective studies should be interpreted cautiously.

In the general population, there is a slight improvement in the survival of patients with septic shock over time [27]. This trend has also been suggested in cancer patients with septic shock. Using the Korean National Health Information Database, Kim *et al.* demonstrated a decrease in 1-year mortality from 84.3% in 2009 to 77.8% in 2017. Unlike pancreatic cancer, patients with lung and stomach cancer experienced continuous improvements in 1-year mortality rates between 2014 and 2019 [28].

Moreover, sepsis may interact with cancer development via an impaired immune response. In a cohort of 1332 patients undergoing gastric surgery for cancer and followed for several years, infectious complications during the postoperative period were associated with increased cancer-specific mortality, with a hazard ratio of 1.84 (95% CI 1.13–2.99). This finding was particularly associated with advanced stage cancer complications, with infectious complications due to anastomotic leakage linked to poor cancer-specific survival [29].

In summary, the 1-year mortality rate of cancer patients admitted to ICU for septic shock appears to be approximately 75% (Table 1). The causes of death remain unclear, but the interplay between septic shock and cancer seems to be deleterious. With the recent dramatic expansion of the therapeutic arsenal for cancer, cancer is tending to become a chronic disease, and a decrease in 1-year mortality among these patients should be expected. Finally, it is noteworthy that in the literature, with few exceptions, the maximum follow-up was 6 months to 2 years, emphasizing the need for studies focusing on long-term outcomes.

## Long-term outcomes not related to mortality

Hospital and ICU readmissions are more prevalent among cancer patients with sepsis than in noncancer patients with sepsis [18] Of 178 017 sepsis survivors, cancer was associated with an increased risk of readmission due to recurrent sepsis and 1-year mortality [30]. A Canadian study found a high level of frailty and functional impairment upon ICU discharge among patients with hematological malignancies, with progressive improvements until reaching a plateau at 6 months [21]. However, the need for consent reduced the number of patients with cognitive impairments, potentially influencing the findings of this study. At 1 year, all components of SF-36 measurements, except physical activity, were decreased compared with patients hospitalized for acute respiratory distress syndrome [31]. In a multicenter cohort of 253 metastatic patients, including 46% of patients with infection, 37% returned home 3 months after ICU discharge [32▪]. Based on a study of 23 solid cancer patients using SF-36 measurements, Toffart *et al.* [33▪] suggested that an ICU stay had no negative impact on quality of life; however, only a few patients were admitted for sepsis in this small cohort.

The long-term outcomes of ICU patients are characterized by the risk of developing postintensive care syndrome (PICS), which refers to a set of symptoms appearing up to 1 year or longer after an ICU stay. PICS is defined ‘as new or worsening



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**Table 1.** Long-term outcome, cancer and sepsis

| Authors [ref] | Type of cancer (number of patients) | Type of sepsis if available | Mortality at |
|---|---|---|---|
| Van de Louw *et al.* [12] | All cancers ($n=119\,379$) | Sepsis ($n=2560$)<br>Severe sepsis ($n=477$)<br>Septic shock ($n=1331$) | 1 year: 35.5% |
| Munshi *et al.* [21] | Hematologic malignancies ($n=414$) | No specific sepsis<br>Sepsis: 40% | 1 year: 79% |
| Camou *et al.* [23] | Hematologic malignancies ($n=119$)<br>Solid cancer ($n=133$) Noncancer ($n=244$) | Septic shock | 6 months:<br>51% for hematologic malignancies<br>68% for solid cancer<br>44% noncancer |
| Cuenca *et al.* [24] | Cancer ($n=132$) including hematologic malignancies ($n=66$)<br>Solid tumor ($n=66$) | Sepsis and vasopressors | 1 year: 83.3% |
| Awad and Nazer [25] | Cancer ($n=1408$)<br>494 discharged alive from ICU and 326 with solid cancer | Septic shock (sepsis and vasopressor) | 1 year: 83.2% |
| Kim *et al.* [28] | Cancer ($n=43\,466$) including<br>90% solid cancer<br>10% hematologic malignancies | Septic shock | 1 year: 81.3% |
| Gonzalez *et al.* [32▪] | Metastatic cancer ($n=253$) | Infection in 46% of patients | 1 year: 71.5% |
| Kim *et al.* [22] | Cancer ($n=5449$) | Septic shock | 2 year: 85.1% |

impairment in physical, psychological/psychiatric and/or cognitive status following an ICU stay, which may limit activities, impair quality of life and functional status and impede the social and professional reintegration of patients' [34]. We identified a retrospective study exploring PICS among gynecologic cancer patients requiring ICU, although they were not admitted for sepsis. In this study, 60% of 111 patients developed at least one risk factor for PICS, consistent with findings from a previous observational, prospective, multicenter study in 16 Japanese ICUs [35]. Notably, 15.3% of these patients required consultations with psychiatrists or social workers, suggesting that preventable measures could improve the outcomes of these patients [36].

In contrast, limited data suggests that sepsis may exacerbate the course of cancer. Survivors of sepsis may exhibit either an hyperinflammatory response or immunosuppression phenotype. Interestingly, in a cohort of 483 sepsis survivors, compared with those with a normal phenotype, patients with sepsis had an increased risk of 6-month readmission or mortality attributable to cancer, with a hazard ratio of 5.15 (95% CI 1.25–21.18) [37]. Recent data from the Swedish Intensive Care Registry from 2005 to 2015, including 37 843 patients with sepsis or septic shock, highlighted an increased risk of new cancer among 18 550 survivors, with an OR of 1.74 (95% CI 1.61–1.88) in women and 1.31 (95% CI 1.23–1.40) in men [38▪▪]. In contrast, in an experimental study using sepsis-trained macrophages, Broquet *et al.* [39▪▪] identified a network of chemokines that induced a decreased risk of tumor development, suggesting that sepsis-trained macrophages were protective against cancer development. Interestingly, nonseptic inflammation did not provoke the same effect.

## Agenda for research

Despite a large number of observational studies, a comprehensive understanding of the quality of life of cancer patients surviving ICU stays is still lacking. While short-term outcomes have been the main focus in recent decades, the emergence of new cancer treatments prompts us to devise strategies for enhancing long-term outcomes. To the best of our knowledge, limited data are available on potential interventions affecting the long-term outcomes of cancer patients with sepsis. For example, early management of potential organ dysfunction or the dysfunction itself may constitute an intervention leading to improved outcomes. Indeed, among 525 critically ill cancer patients, 40% of whom had developed sepsis, early ICU admission was associated with improved 1-year outcomes [40].

Acute renal failure also adversely affects the outcomes of cancer patients developing sepsis or septic shock. In a registry study, Kim *et al.* [22] identified a

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population of 5449 (12.8%) cancer patients requiring renal replacement therapy among 42 477 cancer patients with septic shock. Renal replacement therapy was associated with an increased risk of mortality, with an adjusted hazard ratio of 1.35 (95% CI 1.31–1.40). Thus, early renal protection should be considered to improve the outcomes of these patients.

Monoclonal antibodies used in immunotherapy aim to take the 'brakes' off the immune system and have been associated with low rates of infections. Interestingly, anti-PD-1/PD-L1 agents are included in the arsenal of future therapies for sepsis and septic shock [41,42]. As suggested by Mirouse *et al.* [43], the use of checkpoint inhibitor antibodies could reverse the cell exhaustion induced by septic shock and thus potentially improve the quality of life of cancer patients with septic shock. Further studies are necessary to test this hypothesis.

## CONCLUSION

It is anticipated that sepsis and cancer will be increasingly associated in the coming years. As the short-term mortality of the cancer patients with sepsis has shown improvement over the last decade, it is imperative to investigate the long-term outcomes of these patients, especially considering that cancer is evolving into a chronic disease. Currently, there is a paucity of data regarding outcomes after 1 year, underscoring the need to establish long-term follow-up protocols in this population.

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### Conflicts of interest

*A.B. and D.M. report no conflicts of interest. M.L., Viatris.*

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